Review Article

Tutorial Review: Simulation of Oscillating Chemical Reactions Using Microsoft Excel Macros

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Oscillating reactions are one of the most interesting topics in chemistry and analytical chemistry. Fluctuations in concentrations of one the reacting species (usually a reaction intermediate) create an oscillating chemical reaction. In oscillating systems, the reaction is far from thermodynamic equilibrium. In these systems, at least one autocatalytic step is required. Developing an instinctive feeling for how oscillating reactions work will be invaluable to future generations of chemists. Some software programs have been released for simulating oscillating systems; however, the algorithm details of such software are not transparent to chemists. In contrast, function of spreadsheet tools, like Microsoft Excel, is well understood, and the software is nearly universally available. In this work, the simulation and visualization of different oscillating systems are performed using Microsoft excel. The simple repetitive solving of the ordinary differential equation of an autocatalytic reaction (a spreadsheet row) followed by time, easily automated by a subroutine (a "Macro" in Excel), readily simulates an oscillating reaction. This permits the simulation of some oscillating systems such as Belousov-Zhabotinsky. The versatility of an easily understandable computational platform further enables the simulation of the effects of linear and nonlinear parameters such as concentrations of reactants and catalyst, and kinetic constants. These parameters are readily changed to examine their effects.

INTRODUCTION

Oscillating processes are the basis of life. A well-known theme in biology is the circadian cycle, synchronized to the light-dark periods of the earth. A great number of other biological oscillations have been identified such as glycolytic oscillations in yeast and muscles, hormone cycles, and insulin secretion [1,2]. In addition, oscillating process can be seen in a chemical reaction, which is the basis of natural and biological processes. Basically, fluctuations in concentrations of one of the chemical reaction species (usually a reaction intermediate) create an oscillating chemical reaction; such fluctuations are possible periodicity or non-periodicity under specific reaction conditions. As an example, a novel self-oscillating polymer was prepared by utilizing the Belousov-Zhabotinsky (BZ) reaction [3-6]. Yoshida *et al*. synthesized hydrogel polymers demonstrating rhythmic swelling-deswelling oscillations by coupling temperature and pH-sensitive poly (*N*-isopropylacrylamide-co-acrylicacid-co-butylmethacrylate) gels with non-linear oscillating chemical reactions. Solution of synthetized polymer showed a harmonic mechanical motion with a constant period [6]. Recently, self-oscillating gels have been considered as novel biomimetic materials [7]. Accordingly, a novel biomimetic walking-gel actuator was designed using self-oscillating polymers and gels. The self-oscillating property makes microgels more attractive for future developments such as microgel assembly, optical

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and rheological applications [3].

Hence, understanding the nature and mechanism of oscillating chemical reactions can help us to obtain information about other oscillating processes, especially biological oscillations. Here, we consider a simple model sequence in which the reaction shown in Eq. (1a) is started with a pure starting material A. Autocatalysis is a key feature of most chemical systems exhibiting oscillations, which means the concentration of species increases the rate of the growth of that species [8]. If the reaction product X catalyzes a second faster reaction pathway, Eq. (1b), so that the reaction will speed up after the fornmation of catalyst X [9,10].

$$A \rightarrow X \tag{1a}$$

$$A + X \rightarrow 2X \tag{1b}$$

$$X + Y \rightarrow 2Y \tag{1c}$$

$$Y \rightarrow B \tag{1d}$$
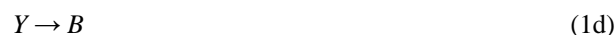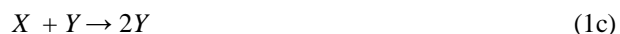
There are some common features in reaction mechanisms of all known chemical oscillators. During the oscillation reaction, an energy releasing occurs. This energy drives the oscillating "side show". In addition, at least two different pathways can be followed in the energy-releasing reaction, and the reaction periodically switches from one pathway to another. In one of these pathways, a certain intermediate is produced, while in another pathway it is consumed, and the concentration of this intermediate acts as a "trigger" for switching from one pathway to the other. When the concentration of the intermediate is low, the reaction follows the producing pathway, leading to a relatively high concentration of the intermediate (Eq. (1b)). When the concentration of the intermediate is high, the reaction switches to the consuming pathway, and decreasing in concentration of the intermediate occurs (Eq. (1c)). Eventually, the reaction reverts to the producing pathway. The repeatedly switching of reaction from one pathway to the other continues [9,11].

At least the following three requirements must be met by a chemical reaction to be the source of an auto-oscillating system: (a) the reaction system should be far from thermodynamic equilibrium state, *i.e.*, its ∆G (Gibbs free energy difference) should be negative and large. (b) There

should be at least one autocatalytic step in reaction steps. Autocatalytic reactions are chemical reactions in which at least one of the reactants is also a product. In this reaction, the product catalyzes the reaction, *i.e.*, enhances its net rate. (c) At least two steady states are needed under the initial conditions [12]. Even autocatalytic systems can reach to a steady state, in which the net rate of the increase of all relevant species is zero. In other words, the rate of reproduction of species equals to the rate of consumption of that species. It is possible to find mathematically by solving the resultant algebraic equations for the concentrations after setting all the time derivatives is equal to zero. A steady state is not necessarily stable and the system evolves away from this state by the small perturbations or fluctuations always existing in a real growing system [8].

The first report documented about oscillation of a chemical system gets back to 1828 by Fechner who described an electrochemical cell that produced an oscillating current. Periodically increasing and decreasing the rate of chromium dissolution in acid was observed by Ostwald in 1899. The best-known model of this type is today called the Lotka-Volterra model which is mostly used to characterize predator-prey interactions, developed by Lotka and Volterra in 1920. William C. Bray at the University of California, Berkeley, and later Bray's student, Herman Liebhafsky, studied the first homogeneous isothermal chemical oscillating reaction of iodate, iodine, and hydrogen peroxide [8]. The other known oscillating reaction is the BZ reaction. The mechanism of the BZ reaction was described by Boris Belousov in 1951, and the basic frame work of its model (Oregonator) was suggested by Field, Koros and Noyes in 1972, and elaborated by Edelson *et al*. Finally the last model was proposed by Prigogine and Lefever in 1968 and dubbed the "Brusselator" by Tyson in 1973 [8]. After that, different oscillating reactions were developed, and their mechanisms were studied. In addition, several methods such as spectrophotometry, potentiometry, and luminescence were used as a monitoring method to investigate the oscillating reactions. Among the luminescence methods, chemiluminescence has been employed as a usual method in monitoring of oscillating reactions [11].

There are two main advantages to perform a simulation rather than actually building the design and testing it. First,

simulation testing is mostly cheaper and faster than performing multiple design tests each time. The second significant advantage of a simulation is the level of detail that you can get from a simulation. A simulation can give results that are not experimentally measurable with our current level of technology. Various attempts have been made to simulate or model the oscillating reactions. A. B. Rovinskii and A. M. Zhabotinsky proposed a mechanism for a self-oscillating reaction in the bromate-ferroin-bromomalonic acid system. The corresponding system of seven differential equations is reduced to a two-component model. The model concepts correspond well to the experimental data [8]. According to the Field-Koros-Noyes mechanism and the Oregonator model in the computational simulation of the BZ oscillating chemical reaction by differential kinetic methodology, the change in the concentrations of $HBrO_2$, bromide ion, and cerium ion are simulated by Jie Ren, Jin Zhang Gao, and Wu Yang. They also studied the effect of variables and parameters, especially the rate constant, on the oscillation curve [13]. Monika Sharma and Praveen Kumar used the Lotka-Volterra model to illustrate chemical oscillations with the help of a computer program [14]. Daniel E. Zaka, Jorg Stelling and Francis J. Doyle described a method for determining the sensitivity of the period to the model parameters that is straightforward to implement and interpret [15].

Despite mass production of "simulations" in the literature, we still believe that they are not intelligible and enough usable for beginners Therefore simulation of the systems in a simple and accessible environment is of great importance and can help beginner chemists.

One of the spreadsheet applications developed by Microsoft is Microsoft Excel. It has a grid of cells arranged in letter-named columns and numbered rows for organizing data manipulations. It allows sectioning of data to view its dependencies on various factors from different perspectives. Microsoft Excel has a programming ability, Visual Basic for Applications (VBA). This ability allows the user to employ a wide variety of numerical methods, *e.g.*, solving differential equations of mathematical physics. The Macro Recorder is a common and easy way to generate VBA code. It records actions of the user and generates VBA code in the form of a macro. Running the macro lets users repeat those

actions automatically. Different trigger types like keyboard shortcuts can also be linked to macro and permits users to easily execute it. In addition, the VBA code of the macro can be edited by the user [16,17].

Few people have done more to demonstrate the capabilities of spreadsheets, specifically MS Excel, for scientific data analysis than analytical chemists [9,17,18]. De Levie extensively demonstrates the use of Excel to elucidate different chemical processes. A. Kadjo and P. K. Dasgupta readily simulated chromatography by a subroutine (a "Macro" in Excel) using the simple repetition of an equilibration process [19].

The aim of this work is to simulate different oscillating chemical reaction models using a simple and easily run software. Hence, Microsoft Excel was used for its simplicity and universal availability.

SIMULATING OSCILATING REACTIONS

To simulate an oscillating chemical reaction, the model for a chemical reaction must be known. Each model consists of the following parts: a chemical mechanism, a set of rate equations for the defined mechanism, and a set of concentration-time equations for the components.

A chemical mechanism is the main part of a chemical reaction model. It consists of some elementary chemical reactions necessary for the description of how reactants produce intermediates and then intermediates combine with one another and the reactants. Finally, the products are formed. After defining the chemical mechanism, it is possible to get rate equations. Rate equations are differential equations corresponding to the reaction mechanism and yielding the rates of change of all species (reactants, intermediates and products) using predefined rate constants and initial concentrations. These ordinary differential equations can be solved using explicator numerical integration methods to get concentration- time equations. These equations describe the concentrations of species as functions of time [20].

Ordinary Differential Equations and Numerical Solution

Using kinetic theory, the concentration-time equations of the species in a reaction mechanism can be defined by a

system of ordinary differential equations (ODEs). Integration of ODEs to any time point allows to calculate the concentration profiles corresponding to data acquisition times with knowledge of the initial conditions. Explicitly integration of the resulting system of ODEs is possible for the simple systems such as the first- and second-order reactions. However, this type of integration is not possible for the majority of multiple step reaction mechanisms such as oscillating chemical reactions. In such cases, numerical integration is a good alternative. Numerical integration allows us to approximate the explicit solution to be calculated for any system of ODEs, within limits of numerical accuracy. Euler's method is a routine numerical integration method. This method uses a form of the Taylor series expansion truncated to the first derivative [21]. Starting with the concentration at time t_{i-1}, the concentration at t_i is estimated using the derivative at t (Eq. (2)).

$$c(t_i) = c(t_{i-1}) + \frac{dc(t)}{dt} \Delta t \qquad (2)$$

It is clear that the accuracy of the approximation is strongly dependent on the size of increment magnitude (Δt) and the function shape. As an example, for the simple second order reaction (Eq. (3a)), ODEs for the components of X, Y and Z can be formulized as Eqs. (3b), (3c) and (3d). In addition, Eqs. (3e), (3f) and (3g) show the equations applied to calculate the concentration profiles of species X, Y and Z.

$$X + Y \overset{k}{\rightarrow} Z \qquad (3a)$$

$$\frac{dc_X}{dt} = -kc_X c_Y \qquad (3b)$$

$$\frac{dc_Z}{dt} = kc_X c_Y \qquad (3c)$$

$$\frac{dc_Y}{dt} = -kc_X c_Y \qquad (3d)$$

$$c_X(t_i) = c_X(t_{i-1}) - kc_X c_Y \Delta t \qquad (3e)$$

$$c_Z(t_i) = c_Z(t_{i-1}) + kc_X c_Y \Delta t \qquad (3f)$$

$$c_Y(t_i) = c_Y(t_{i-1}) - kc_X c_Y \Delta t \qquad (3g)$$

where Δt is time step and equals the difference of t_i and t_{i-1}. Because of low accuracy, it is not usual to use Euler's method as described here in modern numerical integration routines. Some of the modern strategies such as Runge-Kutta and Bulirsch-Stoer methods are used. Those include using higher order terms of the Taylor series expansion or calculating the first derivative at multiple points [21]. The Runge-Kutta methods are a family of implicit and explicit iterative methods used in temporal discretization for the approximate solutions of ordinary differential equations. This method was developed around 1900 by the German mathematicians C. Runge and M. W. Kutta as follows [22].

$$\frac{dy}{dt} = f(t, y), \qquad y(t_0) = y_0 \qquad (4)$$

where, y is an unknown function of time, t, which we would like to approximate. dy/dt is the rate at which y changes as a function of t and of y itself. At the initial time t_0 the corresponding y-value is y_0.
For a step-size Δt ($\Delta t > 0$), we can define

$$y_{i+1} = y_i + \frac{\Delta t}{6}(T_1 + 2T_2 + 2T_3 + T_4) \qquad (5a)$$

$$t_{i+1} + t_i + \Delta t \qquad (5b)$$

$$T_1 = f(t_i, y_i) \qquad (5c)$$

$$T_2 = f(t_i + \frac{\Delta t}{2}, y_i + \frac{\Delta t}{2}T_1) \qquad (5d)$$

$$T_3 = f(t_i + \frac{\Delta t}{2}, y_i + \frac{\Delta t}{2}T_2) \qquad (5e)$$

$$T_4 = f(t_i + \Delta t, y_i + \Delta t T_3) \qquad (5f)$$

Here y_{i+1} is the fourth order Runge-Kutta method approximation of $y(t_{i+1})$, and the next value is determined by the present value (y_i) plus the weighted average of four increments, where T_1 is the increment based on the slope at

the beginning of the interval; T_2 is the increment based on the slope at the midpoint of the interval; T_3 is again the increment based on the slope at the midpoint, and T_4 is the increment based on the slope at the end of the interval. While averaging the four increments, greater weight is given to the increments at the midpoint [22].

In this work, Euler's method is used for numerical solving of ODEs because of its simplicity.

Mechanism of Oscillating Reaction

Lotka-Volterra model. One of the simple models for oscillating reactions was proposed by Lotka in 1920 [23]. This model has not been seen yet in real cases, though it is simple model to understand the oscillating reactions. A series of models derived from Lotka models have been proposed. One of them is Lotka-Volterra model. This model contains two autocatalytic reactions as Eqs. (6a) and (6b):

$$A + X \xrightarrow{k_1} 2X \tag{6a}$$

$$X + Y \xrightarrow{k_2} 2Y \tag{6b}$$

$$Y \xrightarrow{k_3} B \tag{6c}$$

The overall balance of the reaction is as $A \longrightarrow B$, where B is the final product. Considering that the concentration of A is constant, the model contains only two variables X and Y and a final product B. The system of differential equations of this model can be written as Eq. (7):

$$\frac{dc_X}{dt} = k_1 c_A c_X - k_2 c_X c_Y \tag{7a}$$

$$\frac{dc_Y}{dt} = k_2 c_X c_Y - k_3 c_Y \tag{7b}$$

$$\frac{dc_B}{dt} = k_3 c_Y \tag{7c}$$

$$\frac{dc_A}{dt} = -k_1 c_A c_X \tag{7d}$$

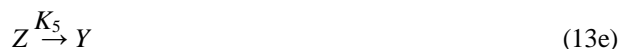In order to obtain concentration-time profiles of X, Y and B, Euler method was used for numerical solving as Eq. (8):

$$c_{X,t_i} = c_{X,t_{i-1}} + \frac{dc_X}{dt}\Delta t = c_{X,t_{i-1}} + \left[k_1 c_A c_{X,t_{i-1}} - k_2 c_{X,t_{i-1}} c_{Y,t_{i-1}}\right]\Delta t \tag{8a}$$

$$c_{Y,t_i} = c_{Y,t_{i-1}} + \frac{dc_Y}{dt}\Delta t = c_{Y,t_{i-1}} + \left[k_2 c_{X,t_{i-1}} c_{Y,t_{i-1}} - k_3 c_{Y,t_{i-1}}\right]\Delta t \tag{8b}$$

$$c_{B,t_i} = c_{B,t_{i-1}} + \frac{dc_B}{dt}\Delta t = c_{B,t_{i-1}} + k_3 c_{Y,t_{i-1}}\Delta t \tag{8c}$$

These equations were used to simulate Lotka-Volterra model of oscillating reaction using Microsoft Excel macro. Since our focus is on intermediate species we avoid bringing the rate equations related to other species in two next models.

The Brusselator Model (Bray-Liebhafsky Model)

The Brusselator model was proposed by Prigogine and his collaborators in 1967 at Free University of Brussels. This model was created for the explanation of the mechanism of Bray-Liebhafsky reaction proposed by Bray and Liebhafsky at University of California, Berkeley [24]. This model is one of the oscillating reactions which can be seen in real cases [25]. The reaction mechanism is as Eq. (9):

$$A \xrightarrow{k_1} X \tag{9a}$$

$$2X + Y \xrightarrow{k_2} 3X \tag{9b}$$

$$B + X \xrightarrow{k_3} Y + P \tag{9c}$$

$$X \xrightarrow{K_4} Q \tag{9d}$$
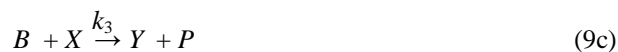
This model contains only one autocatalytic reaction (Eq. (9b)).

Because A = Q, the overall balance of mechanism can be written as Eq. (10):

$$B \longrightarrow P \tag{10}$$

In the case of the Bray reaction, A and Q correspond to HIO_3; B and Y correspond to H_2O_2 and HIO, respectively, and P corresponds to O_2.

The variables of the model are the concentrations of X and Y species. The differential equations of the system are as Eq. (11);

$$\frac{dc_X}{dt} = k_1 c_A + k_2 c_X^2 c_Y - k_3 c_X c_B - k_4 c_X \tag{11a}$$

$$\frac{dc_Y}{dt} = -k_2 c_X^2 c_Y + k_3 c_X c_B \tag{11b}$$

In order to obtain concentration-time profiles of X and Y, Euler method was used for numerical solving as Eq. (12):

$$c_{X,t_i} = c_{X,t_{i-1}} + \frac{dc_X}{dt}\Delta t = c_{X,t_{i-1}} + \left[k_1 c_{A,t_{i-1}} + k_2 c_{X,t_{i-1}}^2 c_{Y,t_{i-1}} - k_3 c_{X,t_{i-1}} c_{B,t_{i-1}} - k_4 c_{X,t_{i-1}}\right]\Delta t \tag{12a}$$

$$c_{Y,t_i} = c_{Y,t_{i-1}} + \frac{dc_Y}{dt}\Delta t = c_{Y,t_{i-1}} + \left[-k_2 c_{X,t_{i-1}}^2 c_{Y,t_{i-1}} + k_3 c_{X,t_{i-1}} c_{B,t_{i-1}}\right]\Delta t \tag{12b}$$

These equations were used to simulate Brusselator model of oscillating reaction using Microsoft Excel macro.

Belousov-Zhabotinsky Oscillating System

The BZ reaction was described by Boris Belousov in 1951. However, 10 years later, Anatol Zhabotinsky could show its oscillatory behavior by addition of the redox indicator ferroin, providing quite visible color changes upon system oscillations [26-28]. Different models have been proposed for BZ oscillating reaction [28,29]. Oregonator model is one of the well understood mechanisms for the BZ reaction [30]. This reaction involves the oxidation of an organic compound (usually malonic acid) by bromate ion in concentrated sulfuric acid. This reaction is catalyzed by traces of transition metal ions that possess two oxidation states differing in a single electron. Various simplified model have been proposed for this reaction. Model contains five steps and three variables as Eq. (13):

$$A + Y \xrightarrow{k_1} X \tag{13a}$$

$$X + Y \xrightarrow{k_2} P \tag{13b}$$

$$B + X \xrightarrow{k_3} 2X + Z \tag{13c}$$

$$2X \xrightarrow{K_4} Q \tag{13d}$$

$$Z \xrightarrow{K_5} Y \tag{13e}$$

Eq. (13c) shows the autocatalytic step of this model. The overall reaction, obtained by adding reactions (13a), (13b), (13d) and twice (13c) and (13e), is as Eq. (14):

$$A + 2B \rightarrow P + Q \tag{14}$$

The usual variable identifications are: A = BrO_3^-, X = $HBrO_2$, Y = Br^-, Z = Ce^{4+}, P = $BrCH(COOH)_2$ or HOBr, and B = $CH_2(COOH)_2$.

The quantities X, Y and Z are dynamic variables corresponding to intermediates, while A and B are reactants whose concentrations are usually assumed to be constant. In addition, P and Q are products.

The system of differential equation for intermediates of the model is Eq. (15):

$$\frac{dc_X}{dt} = k_1 c_A c_Y - k_2 c_X c_Y + k_3 c_X c_B - 2k_4 c_X^2 \tag{15a}$$

$$\frac{dc_Y}{dt} = -k_1 c_A c_Y - k_2 c_X c_Y + k_5 c_Z \tag{15b}$$

$$\frac{dc_Z}{dt} = k_3 c_B c_X - k_5 c_Z \tag{15c}$$

Concentration-time profiles of X, Y and Z can be obtained by numerical solving of differential equations using Euler method as Eq. (16):

$$c_{X,t_i} = c_{X,t_{i-1}} + \frac{dc_X}{dt}\Delta t = c_{X,t_{i-1}} + \left[k_1 c_A c_{Y,t_{i-1}} - k_2 c_{X,t_{i-1}} c_{Y,t_{i-1}} + k_3 c_{X,t_{i-1}} c_B - 2k_4 c_{X,t_{i-1}}^2\right]\Delta t \tag{16a}$$

$$c_{Y,t_i} = c_{Y,t_{i-1}} + \frac{dc_Y}{dt}\Delta t = c_{Y,t_{i-1}} + \left[-k_1 c_A c_{Y,t_{i-1}} - k_2 c_{X,t_{i-1}} c_{Y,t_{i-1}} + k_5 c_{Z,t_{i-1}}\right]\Delta t \tag{16b}$$

$$c_{Z,t_i} = c_{Z,t_{i-1}} + \frac{dc_Z}{dt}\Delta t = c_{Z,t_{i-1}} + \left[k_3 c_B c_{X,t_{i-1}} - k_5 c_{Z,t_{i-1}}\right]\Delta t$$

$$(16c)$$

These equations Eqs. (16a, b and c) were used to simulate Oregonator model of oscillating reaction using Microsoft Excel macro.

EXECUTION

A rather simple "Macro" allows one to simulate these three models in the same way. Here, we explain their simulations.

Lotka-Volterra Model

The initial concentration value of reactant A and rate constants (from K_1 to K_3) for this model are defined in the C3 and from the C5 to C7 cells, respectively. The time step for calculations is defined in cell C4. All these parameters can be changed at will. Then, the initial concentrations of variable species X, Y and B are defined in B11, C11 and D11, respectively. The X and Y species play the role of intermediates in the Lotka-Volterra model, and B is the final product.

In Microsoft Excel, single cells containing values can be defined as a new name other than its address. It is possible by clicking Define Name on the Formulae tab. As an example, the initial concentrations of reactant A in cell C3 was defined A0. This definition process was used to define rate constants and the time step with suitable names as can be seen in the Microsoft Excel file (Appendix 1).

To calculate the concentrations of the intermediates (X and Y) and B at each time step of the reaction, we used Euler's method (a Numerical method) for solving the corresponding differential equations in the Excel worksheet. Hence, we wrote the formulae of Euler's method for X, Y, and B species in B12, C12 and D12, respectively, using Eq. (6). The formulae can be seen by double clicking in the mentioned cells of file. As an example, the formula for calculating the concentration of B is shown in Fig. 1. Two graphs were also prepared to show the concentration of intermediates versus time (graph a in Fig. 1) and versus each other (graph b in Fig. 1).

Writing a subroutine (called a macro in Excel) allows us to carry out as much iteration as we wish each time to execute. To write the macro, we go to the "Developer" tab. (If never previously used, the Developer tab will not show; one would need to go to File\Options\Customize Ribbon and tick the Developer box on the right hand panel). It is
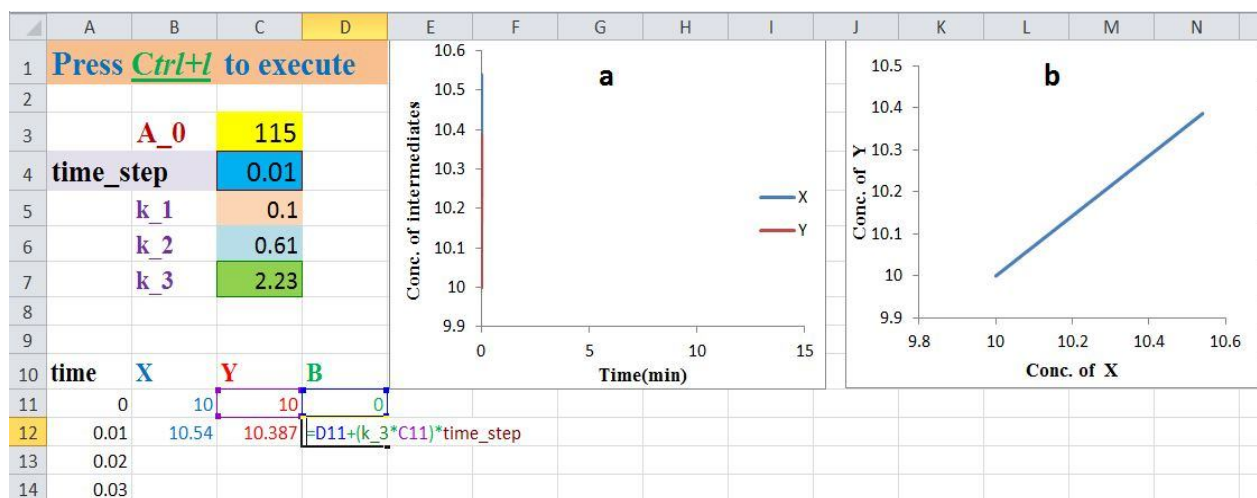
Fig. 1. Initial appearance of the simulation of the Lotka-Volterra model (concentration of the intermediates *vs*. time (a) and *vs*. each other (b)).

worth noting that if the user has not previously used macro, the macro is not run and one should go to the Developer tab\macro security and active the enable all macro options.

Upon clicking "Record Macro," a new dialog box will open. The default name (Macro1) can be left as is or one can choose a name for this subroutine. A code that begins the program is the Ctrl key+an alphabet key (either lower case or upper case); this alphabet key must be now chosen. We choose l, so that when Ctrl+l is entered, the macro will begin execution. Clicking OK will close the dialog box and we can proceed with recording the macro.

The cells B12:D12 are selected and dragged down into the next row (B13:D13), and then the cells B13:D13 are selected and dragged down into the next row (B14:D14). These operations are repeated for the 20 next rows. This is all we need, so by clicking on "Stop Recording," the recording stops. Executing the macro at this point will contain only a very limited time after starting the reaction, while the speed of execution is relatively high; therefore, the macro must be modified. To do so, by clicking the "Macros" button, a dialog box opens (our specific macro will already be highlighted), and by clicking the "Edit"

Fig. 2. The macro window as it appears (a) before and (b) after editing.

button, modification can be started. Then, we change the last cell address in the third line and after "Destination = Range" (D13) into D50 and in the next similar lines into D100, D150, D200,… until D1000 with 50 row increments. Additionally, in order to decrease the speed of execution we can insert pause orders after each iteration. Therefore, the modified macro contains the entire times of reaction and a

suitable execution speed. The modification process of macro 1 is shown in Fig. 2. After this modification our macro, macro 1, is ready to simulate the Lotka-Volterra model of oscillating reaction by pressing Ctrl+l (Appendix 1). Figure 3a shows the oscillating concentration profiles of intermediates X and Y for given values of initial concentration and rate constants. To clearly show the
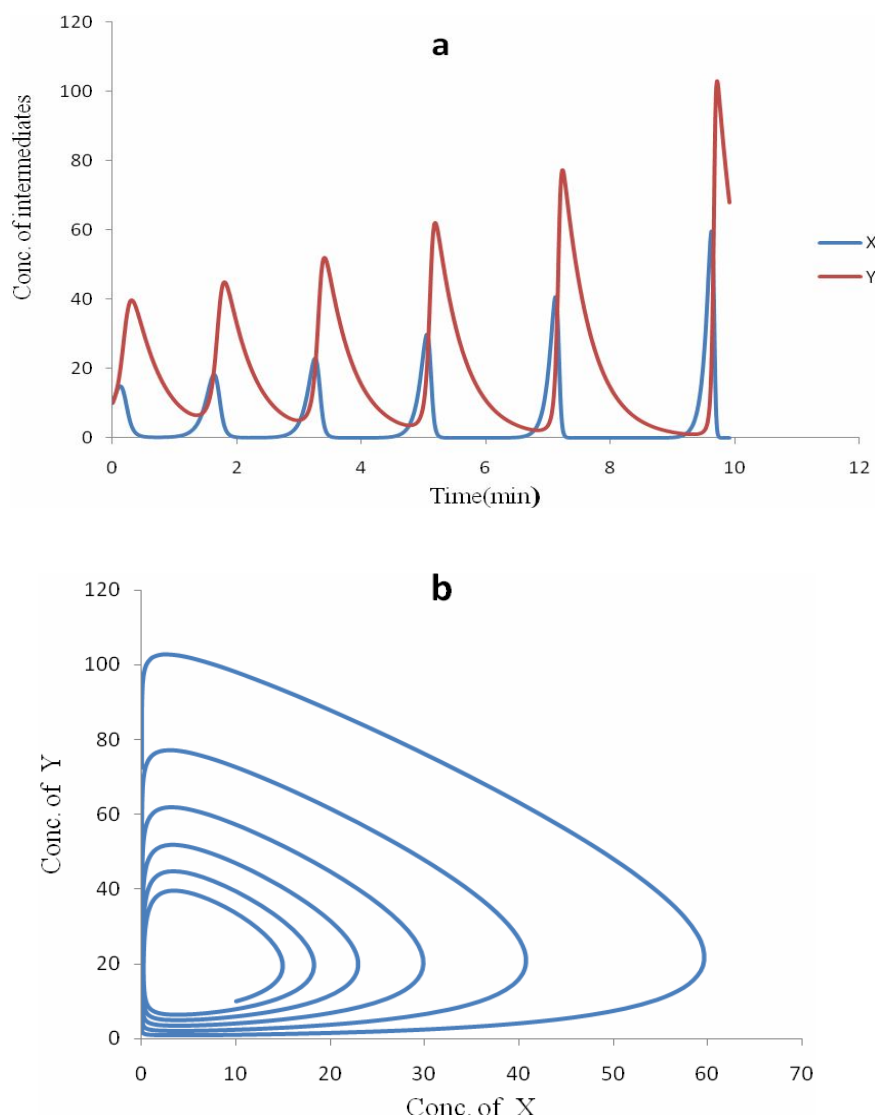
Fig. 3. (a) Oscillating concentration profiles of intermediates X, and Y for given values of the initial Concentration and rate constants and (b) oscillating plot of intermediates X and Y in the Lotka-Volterra model.

oscillating process, the concentration of two intermediates was plotted versus each other, named the oscillating plot, and is shown in Fig. 3b. The oscillating plot shows the concentration effect of the two intermediates on each other and shows how the corresponding reaction speeds up to produce the relative intermediate. In order to easily study the effect of parameters such as rate constants and initial concentration of reactants on simulated oscillating reaction, another Microsoft Excel file was prepared that a has scroll bar for each parameter. Figure 4 shows a snapshot of this file. These scroll bars let the users easily investigate the effect of parameters and visualize these effects. Appendix 2 is a Microsoft Excel file that has scroll bars for each parameters and variables. To add a scroll bar for a parameter in Microsoft Excel, the insert button is selected from the developer tab; a list of different controls will appear. The scroll bar panel will appear in the Microsoft Excel sheet by selecting the scroll bar (form control) button. Linking to the cells and defining scroll parameters is possible by right clicking on the scroll bar panel and selecting format control\control.

We also use the Runge-Kutta method to solve the differential equations of our simplest model (Lotka-Volterra model). At first, the initial concentration value of reactant A, and rate constants (from k_1 to k_3) for this model are defined in the J3 and from the J4 to J6 cells, respectively. The time step for calculations is defined in cell J2. Then, the initial concentrations of variable species X and Y are defined in G11 and L11 respectively. To calculate the concentrations of the intermediates (X and Y) we wrote the formula of Runge-Kutta method for X and Y species in C12:G12 and H12:L12, respectively, using Eq. (5) and rate equations (Eq. (7)). The cells C12:G12 and H12:L12 are selected and dragged down into C1011:F1011 and H1011:L1011. Finally, we draw the concentration figure of X and Y versus time. Appendix 3 is a Microsoft Excel file at which differential equations of Lotka-Volterra model have been solved using Runge-Kutta method and the model has been simulated.

Brusselator Model

Similar to the previous simulation, the initial concentrations of reactants A and B and the rate constants (from k_1 to k_4) for this model are defined in cells C3 and C4

and from J2 to J5, respectively. The time step for the calculations is defined in cell C5. All these parameters can be changed at will; then, the initial concentrations of variable species X, and Y that play the role of intermediates in the Brusselator model are defined in B9 and C9, respectively.

To calculate the concentrations of the intermediates (X and Y) at each time step of the reactions in the Excel worksheet, Euler's method was used. The formulae of Euler's method for X and Y species were written in B10 and C10, respectively, according to Eq. (12).

To write the macro, the Developer tab must be selected. By clicking on Record Macro, a new dialog box will open. The letter r is selected to run the Brusselator model, By clicking on Ok the recording of the macro will start, so that when Ctrl+r is entered, the macro will begin execution.

The cells B10:C10 are selected and dragged down into the next row (B11:C11), and then the cells B11:C11are selected and dragged down into the next row (B12:C12). These operations are repeated for the next 18 rows. By clicking on "Stop Recording," the recording stops. To modify this macro, we click on the "Macros" button and then the "Edit" button. Then, we change the second cell address in the third line and after entering "Destination = Range" (B11) into C120 and the next similar lines into C240, C360, C480, … until C2160 with 120 row increments, and in order to decrease the speed of execution we insert pause orders after each iteration. Therefore, the modified macro contains the entire times of reaction and a suitable execution speed. Appendix 4 is a Microsoft Excel macro file that can be used to simulate the Brusselator model of the oscillating reaction using defined mechanisms and parameters. This macro can be run by the Ctrl+r short cut. Appendix 5 is another Microsoft Excel file that can be used to simulate the Brusselator model of an oscillating reaction. The scroll bar is placed in this file for the initial concentration and rate constants to easily study their effects by the users. Figure 5 shows a print screen from this file. Figure 6 shows the oscillation in concentrations of the intermediates for the given values of rate constants and predefined initial concentration of the reactants.

Belousov-Zhabotinsky Model

The initial concentrations of reactants A and B and rate

constants (from k_1 to k_5) for this model are defined in C2 and C3 and from J1 to J5, respectively. The time step for calculations is defined in cell C4. All these parameters can be changed at will. Then the initial concentrations of variable species Y, X and Z that play the role of intermediates in the Oregonator model are defined in B7, C7 and D7, respectively.

Similar to the previous simulations, to calculate the concentrations of intermediates (Y, X and Z) at each time step of the reactions, the formulae of Euler's method for Y, X and Z species (Eq. (16)) are written in B8, C8 and D8, respectively, in Microsoft Excel worksheet. In addition, two graphs, a and b, are prepared in order to plot the concentration of the intermediates. To write the macro, we
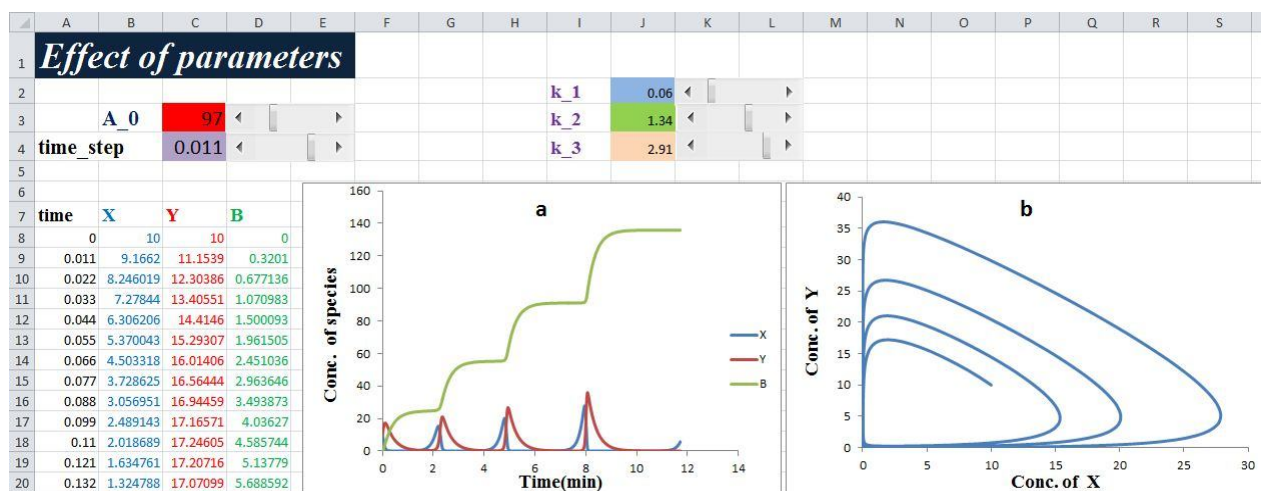
Fig. 4. Evolution the effects of corresponding parameters on oscillating behavior of species of the Lotka-Volterra model by using of scroll bars in the spreadsheet.
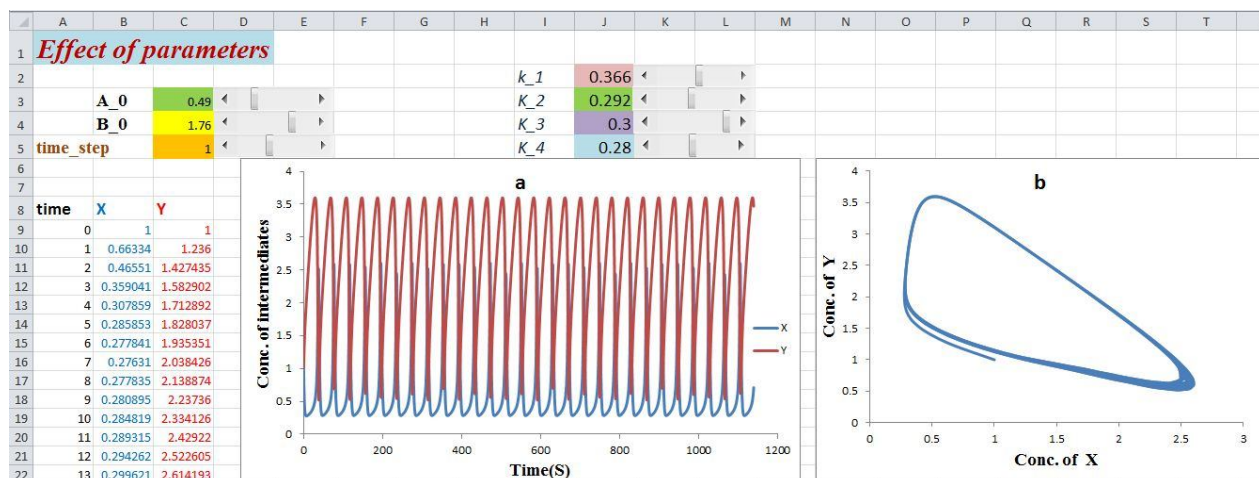
Fig. 5. Evolution the effects of corresponding parameters on oscillating behavior of intermediates of the Brusselator model by using of scroll bars in the spreadsheet.

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go to the Developer tab and click Record Macro. Ctrl+b is chosen as the short cut, so that when Ctrl+ b is entered, the macro will begin execution. By clicking on Ok, the macro recording starts. The cells B8:D8 are selected and dragged down into the next row (B9:D9), and then cellsB9:D9 are selected and dragged down into the next row (B10:D10). These operations are repeated for the next 20 rows. The recording of the macro is stopped by clicking on the "Stop Recording" button. To modify the macro, the second cell

address in the third line and after "Destination = Range" (D9) is changed into D150 and the next similar lines into D300, D450, D600, … until D3000 with 150 increments, and to decrease the speed of the execution, a pause is inserted after each iteration. Similar to the two other simulations, the modified macro contains the entire times of reaction and a suitable execution speed.

Appendix 6 is a Microsoft Excel macro file that can be used to simulate the Oregonator model of BZ oscillating
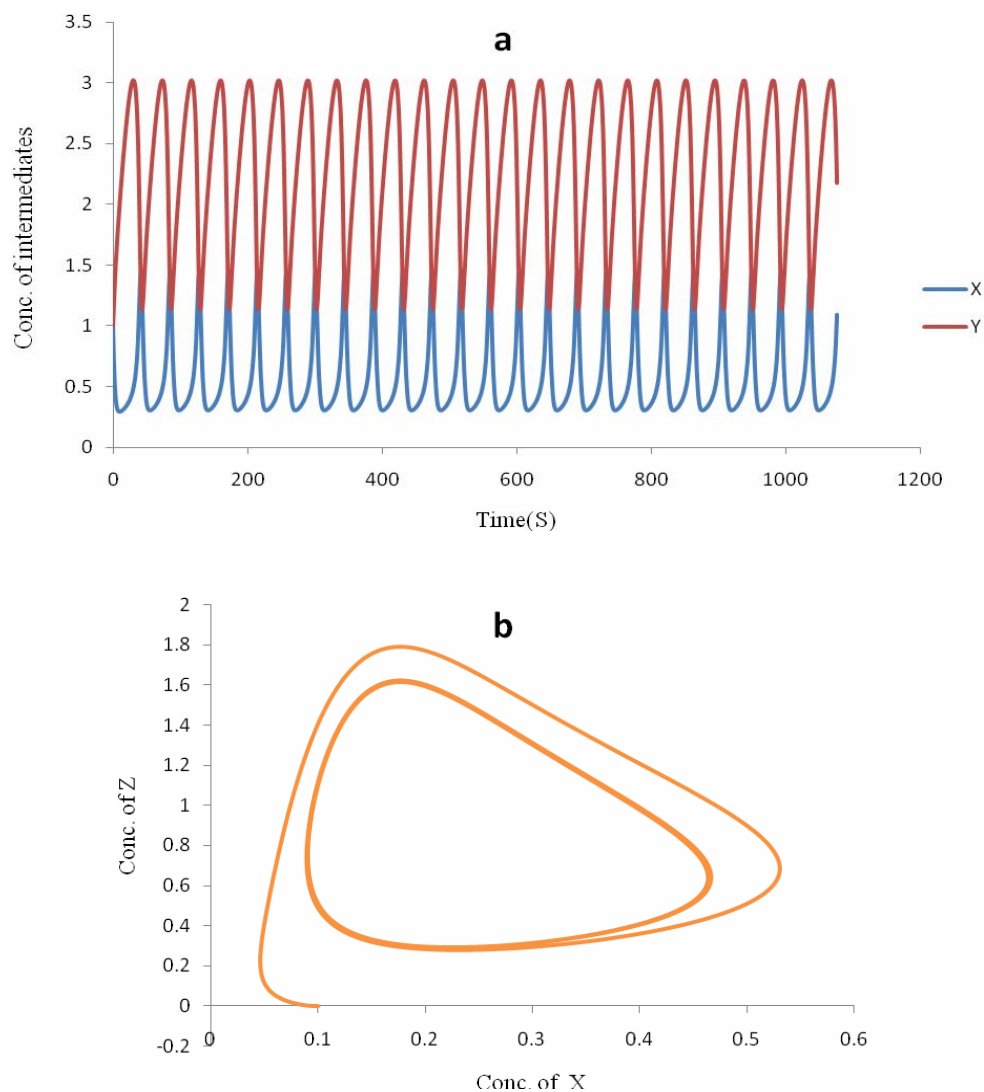
Fig. 6. (a) Oscillating concentration profiles of intermediates X and Y for given values of the initial concentration and rate constants and (b) oscillating plot of the intermediates X and Y in the Brusselator model.

Table 1. Temporal Evolution of Oscillating Behavior for the Intermediates of Oregonator Model with Different Values of K_1 and with Constant Values of: $K_2 = 0.5$; $K_3 = 1$; $K_4 = 0.045$; $K_5 = 0.025$; Time Step = 2.5 s and with Constant Concentration of: $A_0 = 0.05$ M and $B_0 = 0.1$ M
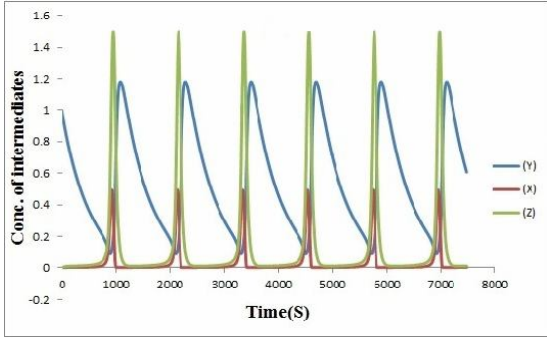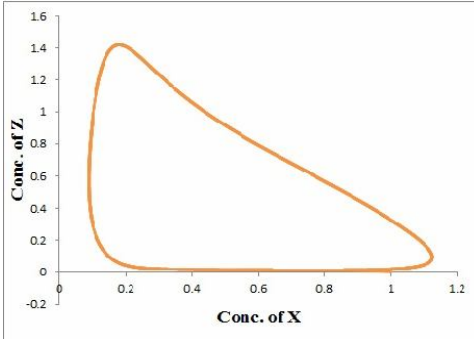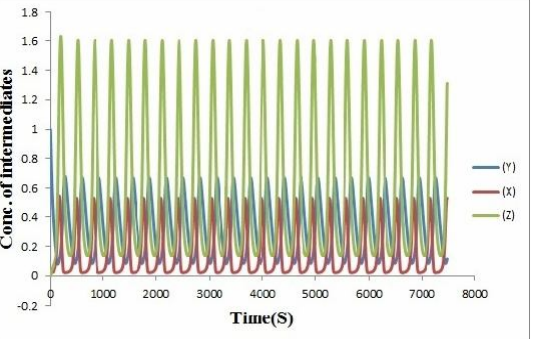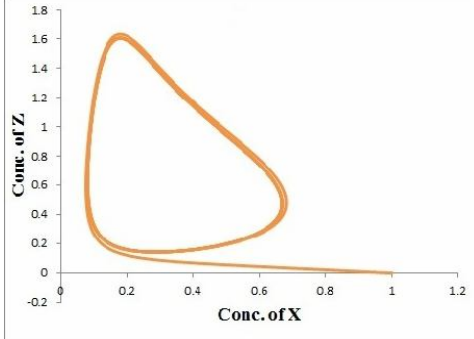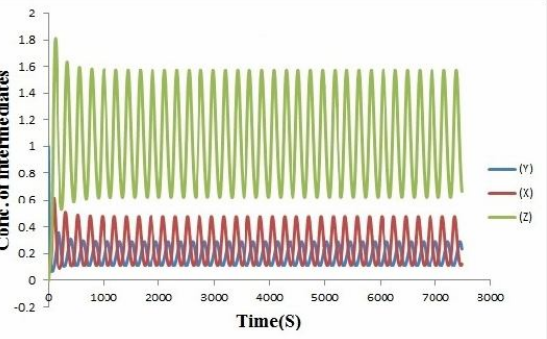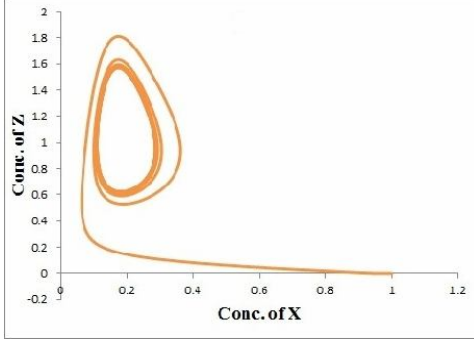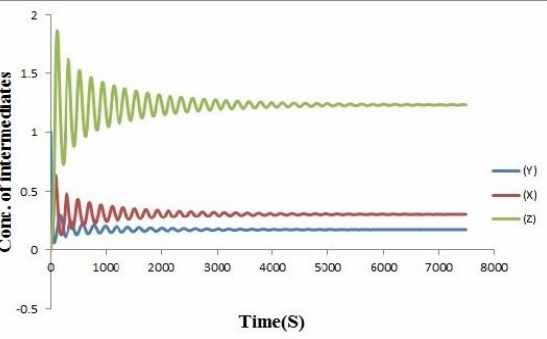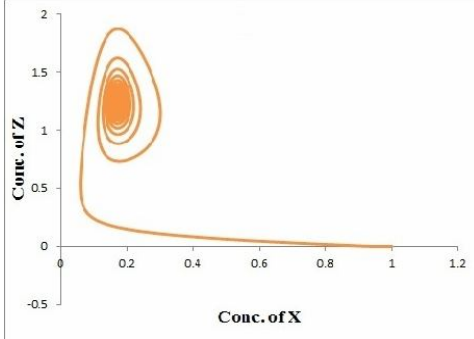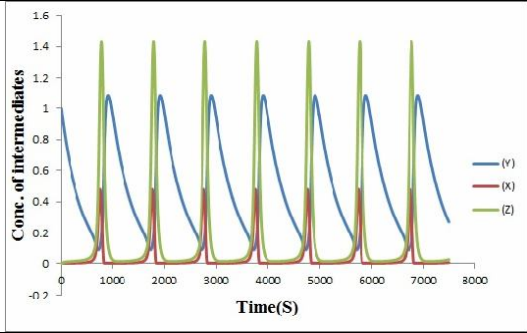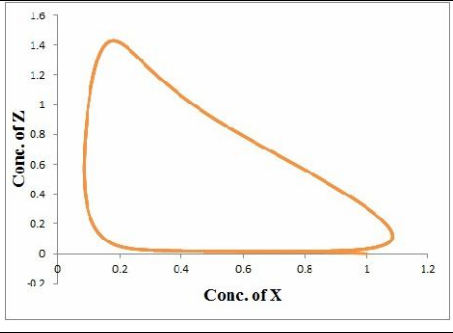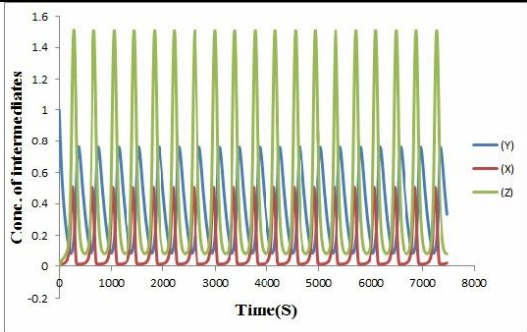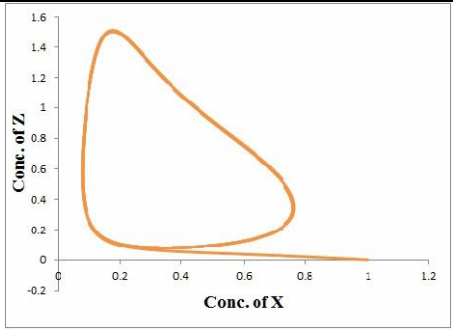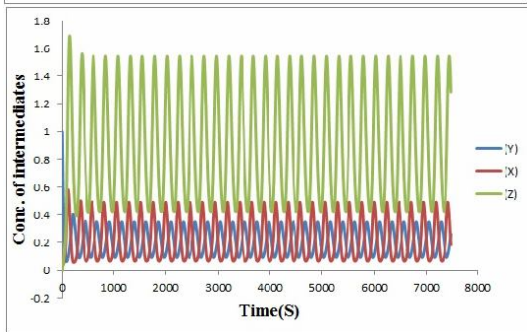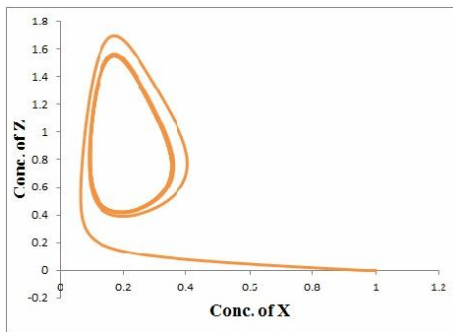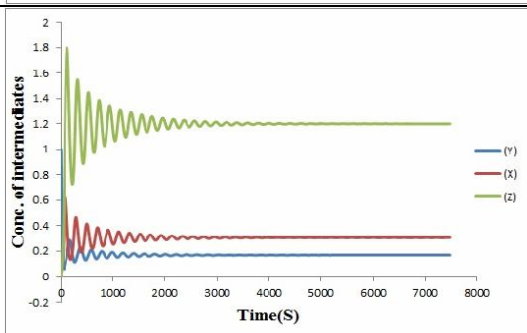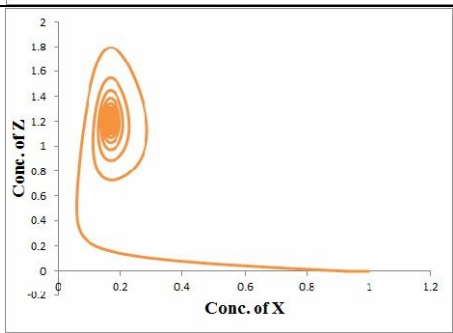
Value of parameters	Concentration profile	Oscillating plot
$K_1 = 0.02$		
$K_1 = 0.15$		
$K_1 = 0.2$		
$K_1 = 0.4$		

Table 2. Temporal Evolution of Oscillating Behavior for the Intermediates of Oregonator Model with Different Values of A_0 and with Constant Values of: $K_1 = 0.15$; $K_2 = 0.5$; $K_3 = 1$; $K_4 = 0.045$; $K_5 = 0.025$; Time Step $= 2.5$ s and with Constant Concentration of: $B_0 = 0.1$ M

Initial concentration of reactant (M)	Concentration profile	Oscillating plot
$A_0 = 0.005$		
$A_0 = 0.02$		
$A_0 = 0.065$		
$A_0 = 0.1$		

reaction using defined mechanisms and parameters. This macro can be run by pressing the Ctrl+b short cut. In another Microsoft Excel file, the scroll bar is placed for the initial concentration and rate constants to easily study their effect (Appendix 7). Table1 shows the simulated concentration profiles of three intermediates X, Y and Z, and the oscillating plot for two intermediates X and Y for different given values of the rate constant of the first step of mechanism, k_1. Other rate constants and initial concentrations are kept constant for the mentioned simulations. To investigate the effect of the initial concentration of reactant A, in the Oregonator model, four

models were simulated with different initial concentrations of A and a constant concentration of other reactants. Table 2 shows the simulated concentration profiles of the three intermediates X, Y and Z, and the oscillating plot for the two intermediates X and Y for different given values of the initial concentration of A.

Nonlinear Least-Squares Curve Fitting with Microsoft Excel Solver

Least squares curve fitting, as a powerful tool that is widely available in spreadsheets, provides a simple means of fitting experimental data to linear and nonlinear
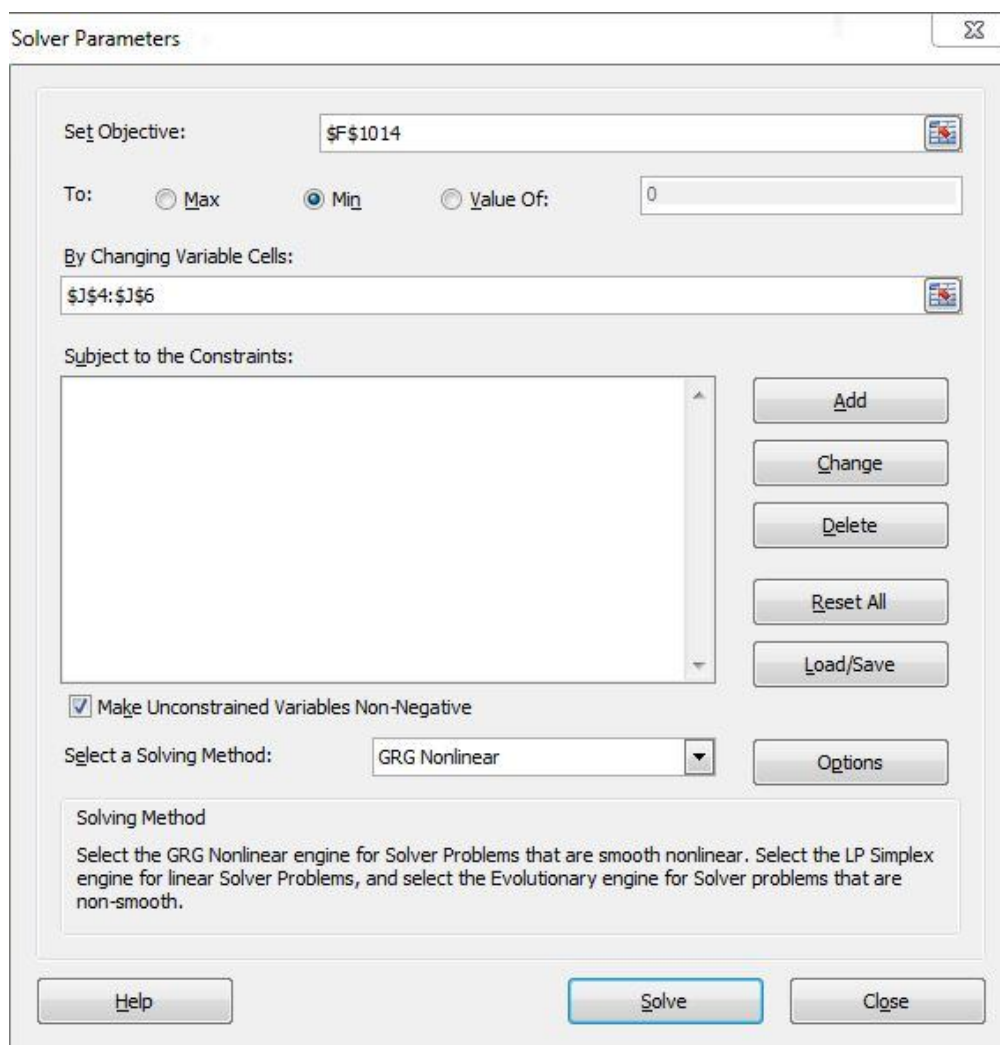
Fig. 7. The solver window.

functions. The procedure is so easy to use and its mode of operation is so obvious that could be an excellent way for the students to learn the underlying principle of least squares curve fitting [31]. With Solver, it is possible to find an optimal (maximum or minimum) value for a formula in one cell-called the objective cell-subject to constraints, or limits, on the values of other formula cells on a worksheet. Solver works with a group of cells, called decision variables or simply variable cells that participate in computing the formulas in the objective and constraint cells. Solver adjusts the values in the decision variable cells to satisfy the limits on constraint cells and produce the result you want for the objective cell. To optimize the parameters such as rate constants, after simulation of models, we can use the solver. For example we perform the fitting for Lotka-Volterra model. Residual defined as Eq. (17).

$$r_i = y_i(observed) - y_i(calculated) \qquad (17)$$

The least squares criterion is to find the values of rate constants using the concentration values of x and y, in Eqs. (6a) and (6b) for each time step, which minimize the sum of square of residuals:

$$SSQ = \sum_{i=1}^{n} (r_i)^2 \qquad (18)$$

where n is the total number of points. The best values of k_1, k_2 and k_3 that minimize the SSQ are found by Solver. To perform the nonlinear least squares curve fitting, the measured data must be pasted in spreadsheet. The concentrations of X and Y which were simulated using Lotka-Voltra model in appendix? were copied and pasted in new spreadsheet as values in B13:B1013 and C13:C1013 for X and Y, respectively. The next step is calculating the concentrations of X and Y using approximately estimated rate constants. The initial concentration value of reactant A and estimated rate constants (from k_1 to k_3) for this model are defined in the J2 and from the J4 to J6 cells, respectively. The time step for calculations is defined in cell J3. Then, the initial concentrations of variable species X and Y are defined in D13 and E13 respectively. To calculate the concentrations of the intermediates (X and Y) we wrote the formulae of Euler's method for X and Y species in D14 and

E14, respectively, using Eq. (6). The cells D14 and E14 are selected and dragged down into the D1013 and E1013. Temporarily assign the values 0.07, 0.8 and 1.3 to k_1, k_2 and k_3, respectively. In column F, sum of squares of X and Y residuals was written in cell F13 and dragged down to F1013. For example, F14 = ((D14 - B14)^2 + (E14 - C14)^2). In cell F1014, sum of the F13:F1013 cells was written and used as SSQ.

The least squares criterion is to find the values of k_1, k_2 and k_3 that minimize the sum in cell F1014. Microsoft Excel provides a tool called Solver that handles this problem in a manner that is transparent to the user. Solver is invoked in different manners by different versions of the software. In version 2010, if the Solver command or the Analysis group is not available, you need to load the Solver Add-in program. By clicking on the solver in Data tab the screen in Fig. 7 appears. If cell F1014 was highlighted prior to calling Solver, then "F1014" automatically appears in the upper left dialog box that says "Set objective". If other cell was highlighted, enter F1014 in the Set objective box. Since we intend to minimize the SSQ, calculated in cell F1014, click "Min" on the second line beside "to". Finally, write "J4, J5 and J6" in the dialog box labeled "By Changing variable Cells". Now click "Solve" and you have just asked the software to set the value of cell F1014 to a minimum by changing the values in cells J4, J5, and J6. After finishing Solver task in a few seconds, the value of J4, J5 and J6 cells changes to 0.1, 1 and 1.5, respectively. When we have only one of the species (X or Y) concentration data the same steps allow us to obtain the optimum values of k1, k2 and k2, k3 by using X and Y concentration values, respectively. Appendix 8 is a Microsoft Excel file that is ready for least squares fitting of rate constants of Lotka-Volterra model. To obtain the optimum values of the rate constants we can use this fitting for two other models.

CONCLUSIONS

The present study describes the simulation of oscillating reaction models in a simple and accessible environment and reveals the capabilities of spreadsheets, specifically Microsoft Excel. The simulations show the oscillating behavior of intermediates concentrations as in real experiments. In addition, the effects of corresponding

parameters specifically species concentrations and rate constants on oscillating behavior are studied very easily and affordably.

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Supplementary Materials

Appendices associated with this article can be found, in online version, analchemres.org.

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